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Signed A M Brewer.

Dated 4 August 1999

Patents Form 1/77

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30 OCT 1998

02NOV98 E401579-1 D00192
P01/7700 0.00 - 9823871.0

# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form))*

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — P.75595 GCW.CMK

2. Patent application number *(The Patent Office will fill in this part)* — **9823871.0**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — Pharmacia & Upjohn S.p.A.
Via Robert Koch 1.2
20152 Milan, Italy

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Italy 7100001001

4. Title of the invention — 2-Amino-thiazole derivatives, process for their preparation, and their use as antitumour agents

5. Name of your agent *(if you have one)* — J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — 14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)* — 26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|
| | | |

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|
| | |

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*
*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body:*
*See note (d))* — Yes

## Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
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| Continuation sheets of this form | |
| Description | 32 |
| Claim(s) | 7 |
| Abstract | 1 |
| Drawing(s) | |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | 2 x 7 |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application

Signature JA Kemp & Co Date 30 October 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

C M KEEN
0171 405 3292

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*c) If there is not enough space for all the relevant details on any part of this form, please continue of a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

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FC 857/5

# 2-AMINO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS

The present invention relates to 2-amino-thiazole derivatives and, more in particular, it relates to 2-amino-1,3-thiazole derivatives, to a process for their preparation, to pharmaceutical compositions containing them and to their use as antitumor agents.

Several cytotoxic drugs such as, e.g. fluorouracil (5-FU), doxorubicin and camptothecins result to damage DNA or to affect cellular metabolic pathways and thus cause, in many cases, an indirect block of the cell cycle.
Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.
In this respect, compounds capable of being highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

It is well known in the art that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk).
In their turn the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.
For a general reference to cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al. in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.
Checkpoint controls are defective in tumor cells due, in part, to disregulation of cdk activity.

For example, altered expression of cyclin E and cdk's has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence of cancer.

Increasing evidence supports the idea that the cdks are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention. In particular, the direct inhibition of cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

It has now been found that the compounds of the invention, hereinafter referred to as 2-amino-1,3-thiazole derivatives, are endowed with cdk/cyclin kinase inhibitory activity and are thus useful in therapy as antitumor agents whilst lacking, in terms of both toxicity and side effects, the aforementioned drawbacks known for currently available antitumor drugs.

In addition, besides of being useful in the treatment of cancer, these 2-amino-1,3-thiazole derivatives are also useful in the treatment of a variety of other cell proliferative disorders such as, for instance, psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis, and in the treatment of Alzheimer's disease.

Several 2-amino-1,3-thiazole derivatives are known in the art. Just few examples among them are 2-acetamido-, 2-propionamido- or 2-butyramido-1,3-thiazole derivatives further substituted by halogen atoms in position 5 of the thiazole ring, which are reported as herbicides in JP 73027467 (Sankyo Co. Ltd.) or US 3,374,082 (The Upjohn Co.); 5-nitro-2-benzamido-1,3-thiazole is reported as pesticide in Ann. Rech. Vet., 22(4), 359-63, 1991; 5-phenyl-2-acetamido-1,3-thiazoles further substituted onto phenyl ring are reported as synthetic intermediates

(Chemical Abstracts, 1980, 92:128793); and 5-dimethylaminomethyl- or 5-diethylaminomethyl-2-acetamido-1,3-thiazole, both reported as herbicides in JP 71018564 (Japan Gas Chem Co.).

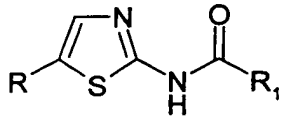
Several other 2-amino-1,3-thiazole derivatives have been reported in the art as useful therapeutic agents.

In particular, 2-benzamido-1,3-thiazoles are disclosed in EP-A-261503 (Valeas S.p.A.) as antiallergic agents; 5-alkyl-2-phenylalkylcarbonylamino-1,3-thiazoles are disclosed in WO 98/04536 (Otsuka Pharmaceutical Co.) as protein kinase C inhibitors; 5-arylthio-2-acylamino-1,3-thiazole derivatives are disclosed in EP-A-412404 (Fujisawa Pharm. Co.) as antitumor agents.

In addition, among the compounds reported in the art as therapeutic agents, DE 2128941 (Melle-Bezons) discloses 2-aminomethylcarbonylamino-5-chloro-1,3-thiazoles as antiinflammatory, sedative and analgesic agents; the compound 2-diethylaminomethylcarbonylamino-5-chloro-1,3-thiazole being specifically exemplified therein.

To the extent of our knowledge, however, none of the known compounds has been reported as cell cycle inhibitor.

Accordingly, the present invention provides the use of a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which

is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating cell proliferative disorders or Alzheimer's disease.

In the present description, unless otherwise specified, with the term halogen atom we intend a fluorine, chlorine, bromine or iodine atom, chlorine and bromine being preferred.

As used herein alkyl and alkoxy stand for $C_1$-$C_6$ alkyl and $C_1$-$C_6$ alkoxy groups. With the term straight or branched $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy group we intend a group selected from, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

With the term $C_3$-$C_6$ cycloalkyl group we intend a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, cyclopropyl being preferred. The term aryl stands for phenyl or for an optionally benzocondensed 5 or 6 membered

aromatic heterocycle with 1 or 2 heteroatoms selected among nitrogen, oxygen and sulphur;

With the term 5 or 6 membered aromatic heterocycle with 1 or 2 heteroatoms selected among nitrogen, oxygen and sulphur, pyrrole, furan, thiophene, imidazole, pyrazole, thiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine or the like, are intended.

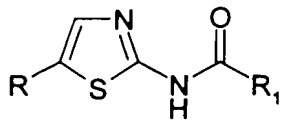
Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as antiinflammatory, sedative and analgesic agents but not as antitumor agents or even as cell cycle inhibitors.

Therefore, it is a further object of the present invention a compound which is a 2-amino-1,3-thiazole derivative of formula (Ia)



(Ia)

wherein

R is a halogen atom or is selected nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

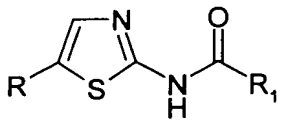
$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof, for use as a medicament;

with the proviso that the compound is not 2-diethylaminomethylcarbonylamino-5-chloro-1,3-thiazole.

Among the compounds of formula (I) above reported, several 2-amino-1,3-thiazole derivatives result to be novel compounds.

Therefore, the present invention further provides a compound which is a 2-amino-1,3-thiazole derivative of formula (Ib)



(Ib)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups;

$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

provided that:

a) when R is a bromine or a chlorine atom then $R_1$ is not $C_1$-$C_4$ alkyl or an optionally substituted aminomethyl;

b) when R is iodine, an ethyl group or a methyl group substituted by phenyl or by dialkylamino, or it is a phenyl group optionally substituted by methyl, ethyl, nitro or halogen atoms, then $R_1$ is not methyl; and

c) when R is nitro then $R_1$ is not phenyl.

From the foregoing it is clear to the man skilled in the art that the novel compounds of the invention of formula (Ib) are within the meanings of the compounds of general formula (Ia) which, in turn, are within the meanings of the compounds of formula (I).

Preferred compounds of the invention of formula (Ib), and thus of formula (Ia) and (I), are the compounds wherein R is a halogen atom, an optionally substituted straight or branched $C_1$-$C_4$ alkyl group, a cycloalkyl, aryl or arylalkyl group, and $R_1$ is an otpionally substituted $C_1$-$C_4$ alkyl group or an optionally substituted phenyl.
Still more preferred compounds, within this class, are the compounds of formula (Ib) wherein $R_1$ is phenyl or a $C_1$-$C_4$ alkyl group substituted by hydroxy, amino, alkoxy, alkoxycarbonyl, phenyl or by a heterocycle such as pyiridine or indole, the phenyl and the heterocycle both being optionally further substituted.

Examples of preferred compounds for use in the invention, whenever appropriate in the form of pharmaceutically acceptable salts, e.g. hydrobromide or hydrochloride, are the following:

ethyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxopropanoate;

N-(5-bromo-1,3-thiazol-2-yl)-2-phenyl-acetamide;

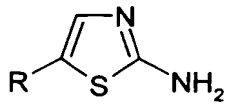
N-(5-bromo-1,3-thiazol-2-yl)-benzamide;

Ethyl 4-[(5-bromo-1,3-thiazol-2-yl)amino]-4-oxobutanoate;

N-(5-Bromo-thiazol-2-yl)-3-hydroxy-propionamide;
N-(5-Bromo-1,3-thiazol-2-yl)-4-hydroxybutanamide;
N-(5-Bromo-thiazol-2-yl)-2-ethoxy-acetamide;
2-N-[2-(3-pyridyl)-acetyl-amino]-5-bromo-thiazole;
2-N-[2-(3-pyridyl)-acetyl-amino]-5-isopropyl-thiazole;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-chorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-chorophenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-phenyl-acetamide;
N-(5-bromo-thiazol-2-yl)-4-sulfamoyl-benzamide;
N-(5-isopropyl-thiazol-2-yl)-4-sulfamoyl-benzamide;
4-amino-N-(5-bromo-1,3-thiazol-2-yl)butanamide;

3-amino-N-(5-bromo-1,3-thiazol-2-yl)propionamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-butanamide;
N-(5-bromo-1,3-thiazol-2-yl)-butanamide;
N-(5-chloro-1,3-thiazol-2-yl)-butanamide;
N-(5-phenyl-1,3-thiazol-2-yl)-butanamide;
N-(5-nitro-1,3-thiazol-2-yl)-butanamide;
N-(5-methyl-1,3-thiazol-2-yl)-butanamide;
N-(5-benzyl-1,3-thiazol-2-yl)-butanamide;
N-(5-isobutyl-1,3-thiazol-2-yl)-butanamide;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-butanamide;
N-{5-[2-(methylsulfonyl)ethyl]-1,3-thiazol-2-yl}-butanamide;
N-[5-(2-methylthioethyl)-1,3-thiazol-2-yl]-butanamide;
N-{5-[2-(methoxycarbonyl)ethyl]-1,3-thiazol-2-yl}-butanamide;
N-[5-(3-methoxy-propyl)-1,3-thiazol-2-yl]-butanamide;
N-[5-(2-ethoxy-ethyl)-1,3-thiazol-2-yl]-butanamide;
N-[5-(indol-3-yl-methyl)-1,3-thiazol-2-yl]-butanamide;
N-[5-(3-oxo-butyl)-1,3-thiazol-2 yl]-butanamide;
and the pharmaceutically acceptable salts thereof.

The compounds of formula (Ib) object of the present invention and the salts thereof can be obtained, for instance, by a process comprising reacting a compound of formula (II)




(II)

with a compound of formula (III)

$R_1$—COX (III)

wherein R and $R_1$ are as defined above and X is hydroxy or a suitable leaving group;
and, if desired, converting a 2-amino-1,3-thiazole derivative of formula (Ib) into another such derivative of formula (Ib), and/or into a salt thereof.

Examples of specific compounds of formula (III) wherein X is a suitable leaving group are those wherein X represents a halogen atom, preferably chlorine or bromine.

It is clear to the man skilled in the art that if the compound of formula (Ib), prepared according to the above process is obtained as an admixture of isomers, its separation into the single isomers of formula (Ib) according to conventional techniques is still within the scope of the present invention.
Likewise, the conversion into the free compound (Ib) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

The above process is an analogy process which can be carried out according to well known methods.
The reaction between a compound of formula (II) and a carboxylic acid of formula (III) wherein X is a hydroxy group, can be carried out in the presence of a coupling agent such as, for instance, carbodiimide, i.e. 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in a suitable solvent such as, for instance, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, 1,4-dioxane, acetonitrile, toluene, or N,N-dimethylformamide at a temperature ranging from about -10°C to reflux for a suitable time, i.e. from about 30 min. to about 96 hours.
The reaction between a compound of formula (II) and a compound of formula (III) can be also carried out, for example, by a mixed anhydride method, using an alkyl chloroformate, such as ethyl, iso-butyl, or iso-propyl chloroformate, in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as, for instance, toluene, dichloromethane, chloroform, tetrahydrofuran, acetonitrile,

diethyl ether, 1,4-dioxane, or N,N-dimethylformamide, at a temperature ranging from about -30°C to room temperature.

The reaction between a compound of formula (II) and a carboxylic acid derivative of formula (III) wherein X is a suitable leaving group can be carried out in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent, such as toluene, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, acetonitrile, or N,N-dimethylformamide, at a temperature ranging from about -10°C to reflux.

Also the optional conversion of a compound of formula (Ib) into another compound of formula (Ib) can be carried out according to known methods.

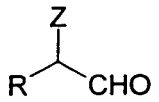
As an example, the nitro group of a compound of formula (Ib) may be converted into an amino group by treatment, for example, with stannous chloride in concentrated hydrochloric acid and by using, if necessary, an organic solvent such as acetic acid, 1,4-dioxane and tetrahydrofuran, at a temperature varying between room temperature and about 100°C.

Likewise, an alkylthio or an arylthio group may be converted into the corresponding alkylsulfonyl and arylsulfonyl group by reaction, for example, with m-chloroperbenzoic acid in a suitable solvent such as dichloromethane or chloroform, at a temperature varying between about -5°C and room temperature.

The optional salification of a compound of formula (Ib) or the conversion of a salt into the free compound as well as the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

The compounds of formula (II) and (III) according to the process object of the present invention are known compounds or can be obtained according to known methods.

For example, a compound of formula (II) wherein R is as defined above can be obtained by reacting a compound of formula (IV)




(IV)

wherein Z is a bromine or chlorine atom, with thiourea in a suitable solvent such as methanol, ethanol, tetrahydrofuran, 1,4-dioxane or toluene, at a temperature varying between room temperature and reflux, for a suitable time ranging from about 1 hour to about 24 hours.

A compound of formula (III) wherein X is a leaving group as defined above can be obtained according to conventional techniques from the corresponding carboxylic acids of formula (III) wherein X is hydroxy.

When preparing the compounds of formula (Ib) according to the process object of the present invention, optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

It is further clear to the man skilled in the art that the above process for preparing the compounds of formula (Ib) can be applied as well to the preparation of the compounds of formula (I) and (Ia) which also include known compounds.

**Pharmacology**

The compounds of formula (I), also encompassing those of formula (Ia) and (Ib), are active as cdk/cyclin inhibitors as they gave positive results when tested according to the following procedure.

The compounds of formula (I) are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the MultiScreen-PH 96 well plate (Millipore), in which a phosphocellulose filter paper was placed at each well bottom allowing binding of positive charged substrate after a washing/filtration step.

When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the filter-bound histone, light emitted was measured in a scintillation counter.

The inhibition assay of cdk2/Cyclin A activity was performed according to the following protocol:

**Kinase reaction:** 1.5 µM histone H1 substrate, 25 µM ATP (0.5 uCi P33g-ATP), 100 ng Cyclin A/cdk2 complex, 10 µM inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, MgCl2 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

**Capture:** 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca++/Mg++ free and filtered by MultiScreen filtration system.

**Detection:** filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and 33P labelled histone H1 was detected by radioactivity counting in the Top-Count instrument.

**Results:** data were analysed and expressed as % inhibition referred to total activity of enzyme (=100%).
All compounds showing inhibition > 50 % were further analysed in order to study and define the kinetic-profile of inhibitor through Ki calculation.
The protocol used was the same described above, except for ATP and substrate concentrations. Either the concentration of ATP and histone H1 substrate were varied: 4, 8,12, 24, 48 µM for ATP (containing proportionally diluted P33g-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 µM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analysed by the computer program "SigmaPlot" for Ki determination, using a random bireactant system equation:

$$v = \frac{Vmax \quad \frac{(A)\ (B)}{aKAKB}}{1 + \frac{(A)}{KA} + \frac{(B)}{KB} + \frac{(A)\ (B)}{aKAKB}}$$

where A=ATP and B=histone H1.

Following the methods described above, a representative compound of the invention which is 2-N-[2-(3-pyridyl)-acetyl-amino]-5-bromo-thiazole showed an inhibiting activity towards the cdk2/cyclin A complex corresponding to 0.14 μM.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.
For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.
The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (Ia), thus encompassing those of formula (Ib), or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).
The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.
For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid,

magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

**Example 1**

**Preparation of Ethyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxopropanoate**

Ethyl malonyl chloride (0.88 ml; 6.99 mmol) was added to a mixture of 2-amino-5-bromothiazole hydrobromide (1.30 g; 5.00 mmol) and Et3N (2.08 ml; 14.94 mmol) in THF (6 ml) at 0-5°C. The mixture was stirred at room temperature overnight, then the reaction was quenched with potassium sarcosinate (0.25 g; 2.00 mmol) and water (12 ml). The product was isolated by filtration as a white solid (0.75 g, 51%): m.p.165-166°C.

$^1$H-NMR ($CDCl_3$) δ ppm: 10.80 (bs, 1H, CONH); 7.38 (s, 1H, thiazole CH); 4.28 (q, J = 7.3 Hz, 2H, COOCH2CH3); 3.56 (s, 2H, COCH2CO); 1.32 (t, J = 7.3 Hz, 2H, COOCH2CH3).

Analogously, the following products can be prepared:

N-(5-bromo-1,3-thiazol-2-yl)-2-phenyl-acetamide

m.p. 206-207°C

$^1$H.NMR (DMSO-$d_6$) δ ppm: 3.76 (s, 2H, COCH2Ph); 7.2-7.3 (m, 5H, Ph); 7.54 (s, 1H, thiazole CH); 12.80 (bs, 1H, CONH);

N-(5-bromo-1,3-thiazol-2-yl)-benzamide

m.p. 126-128°C

$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.90 (bs, 1H, CONH); 8.07, 7.93 (m, 2H, o-Ph hydrogens); 7.63 (s,1H, thiazole CH); 7.62, 7.53, 7.48 (m, 3H, m- and p-Ph hydrogens);

Ethyl 4-[(5-bromo-1,3-thiazol-2-yl)amino]-4-oxobutanoate.

**Example 2**

**Preparation of N-(5-Bromo-thiazol-2-yl)-3-hydroxy-propionamide**

A mixture of LiBH4 (44 mg, 2.02 mmol), ethyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxopropanoate (340 mg, 1.16 mmol), methanol (0.082 ml, 2.02 mmol), and Et2O (50 ml) was refluxed for 20 min. The reaction was quenched with 1 N hydrochloric acid with ice-cooling.

The mixture was then diluted with water and extracted with dichloromethane. The extract was dried and the solvent was evaporated under reduced pressure. Purification by silica gel chromatography (dichloromethane/methanol=98:2 and then 95:5) yielded the title compound as a white solid (0.17 g; 52%).

m.p. 182-184°C (dec.)

$^1$H-NMR ($CDCl_3$) δ ppm: 10.20 (bs, 1H, CONH); 7.35 (s, 1H, thiazole CH); 4.04 (t, J = 5.4 Hz, 2H, COCH2CH2OH); 2.74 (t, J = 5.4 Hz, 2H, COCH2CH2OH).

Analogously, starting from the corresponding ester derivative the following product can be prepared:
N-(5-Bromo-1,3-thiazol-2-yl)-4-hydroxybutanamide.

**Example 3**

**Preparation of N-(5-Bromo-thiazol-2-yl)-2-ethoxy-acetamide**

EDCI (0.53 g, 2.78 mmol) was added to a solution of ethoxyacetic acid (0.29 g, 2.78 mmol) in CH2Cl2 (5 ml) under ice-cooling.

After stirring for 1 h, a solution of 2-amino-5-bromothiazole hydrobromide (0.60 g, 2.31 mmol) and diisopropylethylamine (0.40 ml, 2.34 mmol) in CH2Cl2 (5 ml) was added dropwise, and the entire mixture was kept at 0°C for 1 h, then at room temperature overnight.

The solution was evaporated and the residue partitioned between ethyl acetate and water. The ethyl acetate layer

was further washed with water, 5% citric acid, water, saturated sodium bicarbonate, and water.

Drying over sodium sulfate and evaporation gave a solid which was triturated with isopropyl ether to give the title compound as a beige solid (0.43 g; 70%)

m.p. 100-102°C

$^1$H-NMR ($CDCl_3$) δ ppm: 9.64 (bs, 1H, CONH); 7.38 (s, 1H, thiazole CH); 4.16 (s, 2H, COCH2O); 3.65 (q, J = 6.8 Hz, 2H, OCH2CH3); 1.29 (t, J = 6.8 Hz, 3H, OCH2CH3).

Analogously, the following products can be prepared:

tert-butyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxopropylcarbamate;

Benzyl 4-[(5-bromo-1,3-thiazol-2-yl)amino]-4-oxobutylcarbamate;

2-N-[2-(3-pyridyl)-acetyl-amino]-5-bromo-thiazole

m.p. 232-235°C

$^1$H-NMR (DMSO-$d_6$): 3.82 (s, 2H, COCH2Ph); 7.34 (dd, J=4.4, 7.7 Hz, 1H, H5 Py); 7.55 (s, 1H, thiazole CH); 7.71 (ddd, J=1.6, 2.2, 7.7 Hz, 1H, H4 Py); 8.45 (dd, J=1.6, 4.9 Hz, 1H, H6 Py); 8.49 (d, J=2.2 Hz, 1H, H2 Py); 12.65 (s, 1H, CONH);

2-N-[2-(3-pyridyl)-acetyl-amino]-5-isopropyl-thiazole

m.p. 178-180°C (dec.)

$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.20 (bs, 1H, CONH); 8.45, 7.7, 7.35 (m, 4H, Py); 7.17 (s, 1H, thiazole CH); 3.78 (s, 2H, COCH2); 3.14 (m, 1H, CH(Me)2); 1.22 (s, 1H, MeCHMe); 1.21 (s, 1H, MeCHMe);

N-(5-bromo-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide;

N-(5-bromo-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;

N-(5-bromo-1,3-thiazol-2-yl)-2-(3-chorophenyl)acetamide;

N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-

chorophenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide; and
N-(5-isopropyl-1,3-thiazol-2-yl)-2-phenyl-acetamide
m.p. 135-137°C
$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.18 (bs, 1H, CONH); 7.3 (m, 5H, Ph); 7.18 (s, 1H, thiazole CH); 3.70 (s, 2H, COCH2); 3.13 (m, 1H, CH(Me)2); 1.22 (s, 1H, MeCHMe); 1.21 (s, 1H, MeCHMe).

**Example 4**

**Preparation of N-(5-bromo-thiazol-2-yl)-4-sulfamoyl-benzamide.**

To a mixture of 4-sulfamoylbenzoic acid (1.0 g, 4.97 mmol), Et3N (1.5 ml, 10.78 mmol), DMF (5 ml) and THF (5 ml) isobutyl choroformate (0.70 ml, 5.36 mmol) was added dropwise at -10°C.
After stirring for 1 h, a solution of 2-amino-5-bromothiazole hydrobromide (1,55 g, 5.96 mmol) and Et3N (0.83 ml, 5.96 mmol) in DMF (6 ml) and THF (4 ml) was added dropwise to the mixture at the same temperature.

The resulting mixture was gradually warmed to room temperature over a period of 3 h and then concentrated by evaporation of the solvent in vacuo. To the resultant residue AcOEt and 5% aqueous NaHCO3 were added. The separated organic phase was washed with water, dried over anhydrous Na2SO4, and concentrated under reduced pressure. The residual solid was purified by flash cromatography (dichloromethane/methanol/30% aqueous ammonia=95:5:0.5) to afford the title compound as a yellow solid (0.77 g, 43%)
m.p. 268-270°C
$^1$H-NMR (DMSO-$d_6$) δ ppm: 7.54 (s, 2H, SO2NH2); 7.67 (s, 1H, thiazole CH); 7.94 (d, J=8.8 Hz, 2H, H3 and H5 Ph); 8.21 (d, J=8.8 Hz, 2H, H2 and H6 Ph); 13.10 (bs, 1H, CONH).
Analogously, the following product can be prepared:
N-(5-isopropyl-thiazol-2-yl)-4-sulfamoyl-benzamide
m.p. 222-224°C.

**Example 5**

**Preparation of 4-amino-N-(5-bromo-1,3-thiazol-2-yl)butanamide hydrobromide**

A solution (1.3 ml) of hydrogen bromide in glacial acetic acid (33%) was added to benzyl 4-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxobutylcarbamate (0.72 g, 1.81 mmol) and the mixture was stirred at room temperature for 1 h.
Ether was added and the solid was filtered and washed with ether. The crude product was recrystallized from MeOH/ether to afford the title compound as a beige solid (0.38 g, 61%), m.p. 211-213°C (dec.)
$^1$H-NMR (DMSO-$d_6$) δ ppm: 1.84 (m, 2H, COCH2CH2CH2NH2); 2.53 (t, J=6.8 Hz, 2H, COCH2CH2CH2NH2); 2.81 (m, 2H, COCH2CH2CH2NH2); 7.68 (bs, 3H, NH3+); 12.42 (s, 1H, CONH).

**Example 6**

**Preparation of 3-amino-N-(5-bromo-1,3-thiazol-2-yl)propionamide hydrochloride**

A solution 3.6 N HCl in isopropanol (14 ml) was added to tert-butyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-4-oxopropylcarbamte (0.90 g, 2.57 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residual solid was triturated in ether, filtered and dried in vacuo to afford the title compound as a white solid (0.73 g, quantitative yield)

m.p. 255°C ca.(dec.)

$^1$H-NMR (DMSO-$d_6$) δ ppm: 2.83 (t, J=6.8 Hz, 2H, COCH2CH2NH2); 3.07 (q, J=6.4 Hz, 2H, COCH2CH2NH2); 7.55 (s, 1H, thiazole CH); 7.58 (s, 1H, thiazole CH); 7.96 (bs, 3H, NH3+); 12.58 (s, 1H, CONH).

**Example 7**

**Preparation of N-(5-isopropyl-1,3-thiazol-2-yl)-butanamide**

Triethylamine (0.97 ml; 6.34 mmol) and butanoyl chloride (0.52 ml; 5.07 mmol) were added in this order to a solution of 2-amino-5-isopropyl-1,3-thiazole (0.6 g; 4.23 mmol) in dichloromethane (8 ml), cooled to -5°C.

The reaction mixture was stirred at -5°C for 2 hours and then warmed to room temperature. After additional 4 hours, the organic layer was washed with water, saturated sodium bicarbonate, 1N hydrochloric acid, brine, dried over sodium sulfate and evaporated. The residue was recrystallized from cyclohexane to yield 0.45 g (50%) of the title compound as a colourless solid (m.p. 95-97°C)

$^1$H-NMR (DMSO-$d_6$) δ ppm: 11.82 (s, 1H, CONH); 7.11 (s, 1H, thiazole CH); 3.08 (m, 1H, CHMe2); 2.34 (t, J = 7.1 Hz, 2H, COCH2CH2CH3); 1.58 (m, 2H, COCH2CH2CH3); 1.23 (d, J = 6.6 Hz, 6H, (CH3)2CH); 0.87 (t, J = 7.1 Hz, 3H, COCH2CH2CH3).

Analogously, the following compounds can be prepared:

N-(5-bromo-1,3-thiazol-2-yl)-butanamide

m.p. 163-164°C

$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.27 (bs, 1H, CONH); 7.50 (s, 1H,

thiazole CH); 2.39 (t, 2H, COCH2CH2CH3); 1.59 (m, 2H, COCH2CH2CH3); 0.87 (t, 3H, COCH2CH2CH3);

N-(5-chloro-1,3-thiazol-2-yl)-butanamide

m.p. 170-171°C

$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.25 (bs, 1H, CONH); 7.46 (s, 1H, thiazole CH); 2.38 (t, 2H, COCH2CH2CH3); 1.59 (m, 2H, COCH2CH2CH3); 0.87 (t, 3H, COCH2CH2CH3);

N-(5-phenyl-1,3-thiazol-2-yl)-butanamide

m.p. 183-184°C

$^1$H-NMR (DMSO-$d_6$) δ ppm: 12.13 (s, 1H, CONH), 7.84 (s, 1H, thiazole CH); 7.58 (d, J = 6.8 Hz, 2H, o-Ph hydrogens); 7.39 (dd, J = 6.8 and 7.8 Hz, 2H, m-Ph hydrogens); 7.28 (t, J = 7.8 Hz, 1H, p-Ph hydrogens); 2.41 (t, J = 7.3 Hz, 2H, COCH2CH2CH3); 1.61 (m, 2H, COCH2CH2CH3); 0.89 (t, J = 7.3 Hz, 3H, COCH2CH2CH3);

N-(5-nitro-1,3-thiazol-2-yl)-butanamide

m.p. 175-176°C

$^1$H-NMR (DMSO-$d_6$) δ ppm: 13.02 (s, 1H, CONH); 8.60 (s, 1H, thiazole CH); 2.48 (t, J = 7.3 Hz, 2H, COCH2CH2CH3); 1.62 (m, 2H, COCH2CH2CH3); 0.89 (t, J = 7.3 Hz, 3H, COCH2CH2CH3);

N-(5-methyl-1,3-thiazol-2-yl)-butanamide

m.p. 137-138°C

$^1$H-NMR ($CDCl_3$) δ ppm: 11.89 (s, 1H, CONH); 7.04 (s, 1H, thiazole CH); 2.48 (t, J = 7.3 Hz, 2H, COCH2CH2CH3); 2.41 (s, 3H, CH3); 1.80 (m, 2H, COCH2CH2CH3); 1.02 (t, J = 7.3 Hz, 3H, COCH2CH2CH3);

N-(5-benzyl-1,3-thiazol-2-yl)-butanamide

m.p. 147-149°C

$^1$H-NMR ($CDCl_3$) δ ppm: 7.23 (m, 5H, Ph); 7.07 (s, 1H, thiazole CH); 4.08 (s, 2H, CH2Ph); 2.45 (t, J = 7.8 Hz, 2H, COCH2CH2CH3); 1.76 (m, 2H, COCH2CH2CH3); 0.97 (t, J = 7.8 Hz, 2H, COCH2CH2CH3);

N-(5-isobutyl-1,3-thiazol-2-yl)-butanamide

m.p. 58-60°C

$^1$H-NMR ($CDCl_3$) δ ppm: 7.03 (s, 1H, thiazole CH); 2.61 (d, J = 7.3 Hz, 2H, Me2CHCH2); 2.45 (t, J = 7.8 Hz, 2H, COCH2CH2CH3); 1.81 (m, 1H, Me2CHCH2); 1.78 (m, 2H, COCH2CH2CH3); 1.01 (t, J = 7.8 Hz, 3H, COCH2CH2CH3); 0.95, 0.93 (s, 6H, Me2CHCH2);

N-(5-cyclopropyl-1,3-thiazol-2-yl)-butanamide;

N-{5-[2-(methylsulfonyl)ethyl]-1,3-thiazol-2-yl}-butanamide

m.p. 153-155°C

$^1$H-NMR ($CDCl_3$) δ ppm: 11.01 (s, 1H, CONH); 7.21 (s, 1H, thiazole CH); 3.34 (m, 4H, CH3SO2CH2CH2); 2.90 (s, 3H, CH3SO2); 2.48 (t, J = 7.3 Hz, 2H, COCH2CH2CH3); 1.80 (m, 2H, COCH2CH2CH3); 1.02 (t, J = 7.3 Hz, 3H, COCH2CH2CH3);

N-[5-(2-methylthioethyl)-1,3-thiazol-2-yl]-butanamide

m.p. 67-69°C

$^1$H-NMR ($CDCl_3$) δ ppm: 11.63 (bs, 1H, NHCO), 7.26 (s, 1H, thiazole CH), 3.06 (t, J = 7.0 Hz, 2H, CH3SCH2CH2); 2.77 (t, J = 7.0 Hz, 2H, CH3SCH2CH2); 2.48 (t, J = 7.3 Hz, 2H, COCH2CH2CH3); 2.14 (s, 3H, CH3S); 1.80 (m, 2H, COCH2CH2CH3); 1.02 (t, J = 7.3 Hz, 3H, COCH2CH2CH3);

N-{5-[2-(methoxycarbonyl)ethyl]-1,3-thiazol-2-yl}-butanamide;

N-[5-(3-methoxy-propyl)-1,3-thiazol-2-yl]-butanamide;

N-[5-(2-ethoxy-ethyl)-1,3-thiazol-2-yl]-butanamide;

N-[5-(indol-3-yl-methyl)-1,3-thiazol-2-yl]-butanamide;

N-[5-(3-dimethylaminoimino-butyl)-1,3-thiazol-2-yl]-butanamide.

## Example 8

**2-amino-5-isopropyl-1,3-thiazole**

2 ml (18.6 mmol) of 3-methylbutyraldehyde were dissolved in 15 ml of dioxane. 40.4 ml (18.6 mmol) of a solution 2 % v/v of bromine in dioxane was dropped therein at 0°C.

The mixture was maintained at room temperature under stirring for 2 hours, then 2.83 g (37.2 mmol) of thiourea and 5 ml of ethanol were added.

After 6 hours at room temperature the solution was evaporated to dryness, the residue was dissolved in methylene chloride and the product extracted with 1M hydrochloric acid; the aqueous layer was made basic by using 30% ammonium hydrate and extracted again with methylene chloride. The organic phase was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on a silica gel column, eluting with cyclohexane-ethylacetate to give 1.1 g (42% yield) of the title compound.

$^1$H-NMR (DMSO-$d_6$) δ ppm: 6.6 (s, 2H, NH2); 6.58 (s, 1H, thiazole CH); 2.9 (m, 1H, CHMe2); 1.18 (s, 3H, MeCHMe); 1.17 (s, 3H, MeCHMe).

Analogously the following products can be prepared starting from the suitable aldehyde:

2-amino-5-isobutyl-1,3-thiazole;
2-amino-5-phenyl-1,3-thiazole;
2-amino-5-benzyl-1,3-thiazole;
2-amino-5-(3-indolylmethyl)-1,3-thiazole;
2-amino-5-ethoxyethyl-1,3-thiazole;
2-amino-5-methoxypropyl-1,3-thiazole;
2-amino-5-cyclopropyl-1,3-thiazole;
2-amino-5-methylthioethyl-1,3-thiazole;
2-amino-5-formyl-1,3-thiazole;
2-amino-5-(3-dimethylaminoimino)butyl-1,3-thiazole.

**Example 9**

**4-ethoxy-1-butanol**

85 mg (0.004 mmol) of sodium were dissolved in 50 ml of methanol and 8.7 g (0.23 mol) of sodium borohydride were added. A solution of 4.6 g (0.032 mol) of methyl 4-ethoxy-butanoate in 20 ml of methanol was dropped to the mixture under stirring. The reaction is maintained at reflux for 6 hours, then 300 ml of brine were added and the product was

extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to give 2.25 g (61% yield) of the title compound.

Analogously the following products can be prepared starting from the suitable ester:
2-cyclopropyl-1-ethanol;
3-(3-indolyl)-1-propanol; and
5-dimethylaminoimino-1-hexanol.

**Example 10**

**Methyl 3-(3-indolyl)-propanoate**

2 g (10.57 mmol) of 3-indolepropionic acid were dissolved in 50 ml of methanol. The solution was cooled to 0°C and 5 ml of sulfuric acid 96% were dropped under stirring. The solution was maintained at room temperature overnight and then poured onto ice-water, basified with 30 % ammonium hydrate and finally extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to give 2.3 g of an oily product (93% yield).

Analogously the following products can be prepared starting from the suitable carboxylic acid:
Methyl 4-ethoxy butanoate;
Methyl cyclopropylacetate; and
5-methoxycarbonylethyl-2-amino-1,3-thiazole.

**Example 11**

**4-methyl-pentanal**

1.24 ml (14.18 mmol) of oxalyl chloride were dissolved in 10 ml of methylene chloride and after cooling to -60°C, 2.31 ml of DMSO (35 mmoles) were dropped.
After 5 minutes at the same temperature, a solution of 1 ml (11.9 mmol) of 4-methyl-1-pentanol in 10 ml of methylene

chloride was slowly dropped. The mixture was maintained under stirring for 30 minutes at the same temperature, then 8.3 ml (59.5 mmol) of triethylamine were added. After 2 hours at 0°C water was added. The mixture was diluted with methylene chloride and washed successively with 1M hydrochloric acid, water, saturated sodium bicarbonate and finally with brine. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to give 0.7 g ( 25% yield) of the title compound.

Analogously the following products can be prepared starting from the suitable alcohol:

2-cyclopropyl-1-ethanal;

4-methylthio-1-butanal;

4-ethoxy-1-butanal;

5-methoxy-1-pentanal; and

5-dimethylaminoimino-1-hexanal.

**Example 12**

**5-benzyloxy-1-methoxy-pentane**

1.6 g (0.039 mol)of 55% sodium hydride in oil were added to 50 ml of dimethylformamide under stirring at room temperature. 5 ml (0.026 mol) of 5-benzyloxy-1-pentanol and 2.43 ml (0.039 mol) of methyl iodide were then added successively. After a night the excess of sodium hydride was decomposed with water and the solvent evaporated under vacuum. The residue was redissolved with methylene chloride and washed with water. The organic layer was finally dried over anhydrous sodium sulfate and evaporated to give 3.5 g (70% yield) of the title compound.

Analogously, by using ethyl iodide, the following compound can be prepared:

4-ethoxy-butanoic acid.

**Example 13**

**5-methoxy-1-pentanol**

3.5 g (0.018 mol) of 5-benzyloxy-1-methoxy-pentane were dissolved in 50 ml of ethanol and 400 mg of 10% palladium on activated charcoal were added. The mixture was hydrogenated at 40 psi at room temperature for 5 hours, then filtered on celite and evaporated under vacuum to give 1.77 g (84% yield) of the title compound.

**Example 14**

**Ethyl 5-dimethylaminoimino-hexanoate**

15.8 g (100 mmol) of ethyl 4-acetyl-butanoate and 6 g (100 mmol) of anhydrous N,N-dimethyl hydrazine in 50 ml of toluene containing 0.1 ml of trifluoroacetic acid were heated at 70 °C for 5 hours. The mixture was then washed with water, dried over anhydrous sodium sulfate and evaporated to give 12.3 g (79% yield) of the title compound.

**Example 15**

**N-[5-(3-oxo-butyl)-1,3-thiazol-2 yl]-butanamide**

To a stirred solution of 200 mg (1 mmol) of cupric acetate in 10 ml of water 141 mg (0.5 mmol) of N-[5-(3-dimethylaminoimino-butyl)-1,3-thiazol-2-yl]-butanamide in 10 ml of tetrahydrofuran were added. After 2 hours the solvent was removed under reduced pressure, a mixture of aqueous ammonium chloride and ammonium hydroxide was added and the product extracted with methylene chloride to give after drying and concentration 114 mg (95% yield) of the title compound.

**Example 16**

**2-benzyloxycarbonylamino-5-formyl-1,3-thiazole**

1 g (7.8 mmol) of 2-amino-5-formyl-1,3-thiazole was dissolved in 25 ml of tetrahydrofuran and 1.35 ml (9.36 mmol) of triethylamine and 1.33 ml (9.36 mmol) of benzylchloroformate were added at 0°C under stirring. After

8 hours at room temperature the solvent was evaporated, the residue redissolved with methylene chloride and washed with saturated tartaric acid and then with water. The solvent was dried over anhydrous sodium sulfate and evaporated. The residue was purified by chromatography on silica gel using cyclohexane-ethylacetate as eluent to give 1.3 g (65% yield) of the title compound.

**Example 17**

**5-hydroxymethyl-2-benzyloxycarbonylamino-1,3-thiazole**

530 mg (14 mmol) of sodium borohydride were added in small portions to a stirred solution of 7 g (27 mmol) of 2-benzyloxycarbonylamino-5-formyl-1,3-thiazole in 80 ml of methanol at room temperature. The reaction went on for 2 hours. After evaporation of the solvent the residue was purified by chromatography (cyclohexane-ethylacetate) to give 5.05 g (71% yield) of the title compound.

**Example 18**

**2-benzyloxycarbonylamino-5-(4-phenyl-1-sulfonyloxy)methyl-1,3-thiazole**

To a solution of 1 g (3.78 mmol) of 2-benzyloxycarbonylamino-5-hydroxymethyl-1,3-thiazole in 25 ml of pyridine 0.86 g (4.54 mmol) of tosyl chloride in 10 ml of pyridine were dropped at 0°C. After stirring at room temperature for 6 hours the solvent was evaporated under vacuum, the residue redissolved with methylene chloride, washed with 1M hydrochloric acid and finally with water. The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (cyclohexane-ethylacetate) to give 1.2 g (80% yield) of the title compound.

**Example 19**

**2-benzyloxycarbonylamino-5-(2-ethoxycarbonyl-3-ethoxycarbonylethyl)-1,3-thiazole**

To a suspension of 321 mg of 55% sodium hydride in oil (7.4 mmol) in 20 ml of tetrahydrofuran 1.12 ml (7.4 mmol) of diethylmalonate were added. After 30 minutes, a solution of 1.5 g (3.7 mmol) of 2-benzyloxycarbonylamino-5-(4-phenyl-1-sulphonyloxy)methyl-1,3-thiazole in 10 ml of the same solvent was dropped under stirring. After 6 hours the solvent was evaporated and the residue redissolved with methylene chloride and washed with water. The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (cyclohexane-ethylacetate) to give 1.05 g (70% yield) of the title compound.

**Example 20**

**2-benzyloxycarbonylamino-5-ethoxycarbonylethyl-1,3-thiazole**

To a solution of 4.06 g (10 mmol) of 2-benzyloxycarbonylamino-5-(2-ethoxycarbonyl-3-ethoxycarbonylethyl)-1,3-thiazole in 10 ml of dimethylsulphoxide 0.64 g (11 mmol) of sodium chloride and 0.36 (20 mmol) of water were added under stirring. The mixture was heated at 160 °C for 8 hours and then the solvent removed under vacuum. The residue was redissolved with methylene chloride and washed with brine. After drying and concentration the residue was chromatographed on a silica gel column (cyclohexane-ethylacetate) to give 2.67 g (80% yield) of the title compound.

**Example 21**

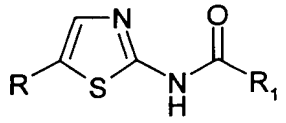
**2-amino-5-carboxyethyl-1,3-thiazole**

1 g (2.9 mmol) of 2-benzyloxycarbonylamino-5-ethoxycarbonylethyl-1,3-thiazole was dissolved in 20 ml of 33% hydrobromic acid in acetic acid. After 2 hours at room temperature, the solvent was evaporated under vacuum. The

residue was redissolved in the minimum amount of water and the hydrobromide of the title compound was precipitated by adding diethylether (75% yield).

**CLAIMS**

**1.** The use of a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

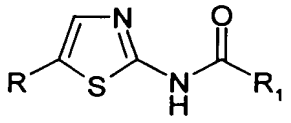
in the manufacture of a medicament for treating cell proliferative disorders or Alzheimer's disease.

**2**. Use according to claim 1 wherein the medicament is for treating tumors.

**3**. Use according to claim 2 wherein the medicament is an antitumour medicament which enables either cell cycle inhibition or cdk/cyclin kinase inhibition.

**4**. Use according to claim 1 wherein the medicament is for treating psoriasis or vascular smooth cell proliferation.

**5**. A compound which is a 2-amino-1,3-thiazole derivative of formula (Ia)



(Ia)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl,

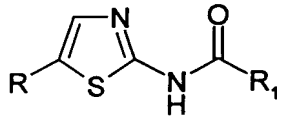
alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof, for use as a medicament;

with the proviso that the compound is not 2-diethylaminomethylcarbonylamino-5-chloro-1,3-thiazole.

**6.** A compound which is a 2-amino-1,3-thiazole derivative of formula (Ib)



(Ib)

wherein

R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulphonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and

$R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R;

or a pharmaceutically acceptable salt thereof;

provided that:

a) when R is a bromine or a chlorine atom then $R_1$ is not $C_1$-$C_4$ alkyl or an optionally substituted aminomethyl;

b) when R is iodine, an ethyl group or a methyl group substituted by phenyl or by dialkylamino, or it is a phenyl group optionally substituted by methyl, ethyl, nitro or halogen atoms, then $R_1$ is not methyl; and

c) when R is nitro then $R_1$ is not phenyl.

**7**. A compound as claimed in claim 6 wherein R is a halogen atom, an unsubstituted or substituted straight or branched $C_1$-$C_4$ alkyl group, a cycloalkyl, aryl or arylalkyl group, and $R_1$ is an unsubstituted or substituted $C_1$-$C_4$ alkyl group or an unsubstituted or substituted phenyl group.

**8**. A compound as claimed in claim 7 wherein $R_1$ is a phenyl or a $C_1$-$C_4$ alkyl group, each of which is unsubstituted or substituted by hydroxy, amino, alkoxy, alkoxycarbonyl or phenyl or by a heterocycle such as pyridine or indole, the phenyl and the heterocycle both being unsubstituted or further substituted.

**9**. A use according to claim 1 or a compound as claimed in claim 5 or claim 6, wherein the 2-amino-1,3-thiazole derivative is selected from:

ethyl 3-[(5-bromo-1,3-thiazol-2-yl)amino]-3-oxopropanoate;

N-(5-bromo-1,3-thiazol-2-yl)-2-phenyl-acetamide;

N-(5-bromo-1,3-thiazol-2-yl)-benzamide;

Ethyl 4-[(5-bromo-1,3-thiazol-2-yl)amino]-4-oxobutanoate;

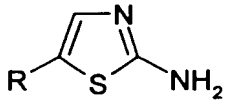
N-(5-Bromo-thiazol-2-yl)-3-hydroxy-propionamide;

N-(5-Bromo-1,3-thiazol-2-yl)-4-hydroxybutanamide;

N-(5-Bromo-thiazol-2-yl)-2-ethoxy-acetamide;
2-N-[2-(3-pyridyl)-acetyl-amino]-5-bromo-thiazole;
2-N-[2-(3-pyridyl)-acetyl-amino]-5-isopropyl-thiazole;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-hydroxyphenyl)acetamide
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3-chorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3-chorophenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(3,4-dihydroxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-methoxyphenyl)acetamide;
N-(5-bromo-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-2-phenyl-acetamide;
N-(5-bromo-thiazol-2-yl)-4-sulfamoyl-benzamide;
N-(5-isopropyl-thiazol-2-yl)-4-sulfamoyl-benzamide;
4-amino-N-(5-bromo-1,3-thiazol-2-yl)butanamide;
3-amino-N-(5-bromo-1,3-thiazol-2-yl)propionamide;
N-(5-isopropyl-1,3-thiazol-2-yl)-butanamide;

N-(5-bromo-1,3-thiazol-2-yl)-butanamide;
N-(5-chloro-1,3-thiazol-2-yl)-butanamide;
N-(5-phenyl-1,3-thiazol-2-yl)-butanamide;
N-(5-nitro-1,3-thiazol-2-yl)-butanamide;
N-(5-methyl-1,3-thiazol-2-yl)-butanamide;
N-(5-benzyl-1,3-thiazol-2-yl)-butanamide;
N-(5-isobutyl-1,3-thiazol-2-yl)-butanamide;
N-(5-cyclopropyl-1,3-thiazol-2-yl)-butanamide;
N-{5-[2-(methylsulfonyl)ethyl]-1,3-thiazol-2-yl}-butanamide;
N-[5-(2-methylthioethyl)-1,3-thiazol-2-yl]-butanamide;
N-{5-[2-(methoxycarbonyl)ethyl]-1,3-thiazol-2-yl}-butanamide;
N-[5-(3-methoxy-propyl)-1,3-thiazol-2-yl]-butanamide;
N-[5-(2-ethoxy-ethyl)-1,3-thiazol-2-yl]-butanamide;
N-[5-(indol-3-yl-methyl)-1,3-thiazol-2-yl]-butanamide; and
N-[5-(3-oxo-butyl)-1,3-thiazol-2 yl]-butanamide.

**10**. A process for producing a compound as defined in claim 6, or a salt thereof, which process comprises reacting a compound of formula (II)




(II)

with a compound of formula (III)

$R_1$–COX (III)

wherein R and $R_1$ are as defined in claim 6 and X is hydroxy or a suitable leaving group;
and, if desired, converting a 2-amino-1,3-thiazole derivative of formula (Ib) into another such derivative of formula (Ib), and/or into a salt thereof.

**11**. A process according to claim 10 wherein, in formula (III), X is hydroxy or a bromine or chlorine atom.

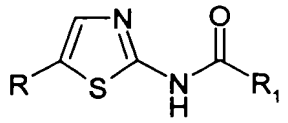
**12.** A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, an effective amount of a compound as defined in claim 5 or 6.

**13.** Use of a compound as defined in claim 5 or 6 in the manufacture of an antitumor medicament which enables either cell cycle inhibition or cdk/cyclin kinase inhibition.

**ABSTRACT**

2-AMINO-THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOUR AGENTS

Compounds which are 2-Amino-1,3-thiazole derivative of formula (I)



(I)

wherein R is a halogen atom or is selected from nitro, amino, alkylamino, hydroxyalkylamino, arylamino, $C_3$-$C_6$ cycloalkyl and straight or branched $C_1$-$C_6$ alkyl which is unsubstituted or substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy or aryl which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups, or R is an aryl group which is unsubstituted or substituted by one or more hydroxy, halogen, nitro, alkoxy, aryloxy, alkylthio, arylthio, amino, alkylamino, dialkylamino, N-alkyl-piperazinyl, 4-morpholinyl, arylamino, cyano, alkyl, phenyl, aminosulfonyl, aminocarbonyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or carboxy groups; and $R_1$ is a straight or branched $C_1$-$C_6$ alkyl group or an aryl group, each being unsubstituted or substituted as defined above for R, or pharmaceutically acceptable salts thereof, are useful for treating cell proliferative disorders and Alzheimer's disease.